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(54) Title: PHARMACEUTICAL FORMULATIONS COMPRISING CLAVULANIC ACID OR DERIVATIVES AND AN ORGANIC ACID OR SALT

(57) Abstract

Pharmaceutical formulations comprising derivatives of clavulanic acid, and their use, particularly solid pharmaceutical formulations for oral administration comprising in combination clavulanate and a pharmaceutically acceptable organic acid or a pharmaceutically acceptable salt-like derivative thereof.

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PHARMACEUTICAL FORMULATIONS COMPRISING CLAVULANIC ACID OR DERIVATIVES AND AN ORGANIC ACID OR SALT

This invention relates to pharmaceutical formulations comprising derivatives of clavulanic acid, and to their use.

Clavulanic acid is a β-lactamase inhibitor, and its pharmaceutically acceptable salts (herein individually and collectively referred to as "clavulanate" unless specific salts are identified) may be formulated in antibacterial medicament formulations with antibiotics, particularly β-lactam antibiotics, to increase their resistance to the β-lactamase enzymes produced by certain microorganisms. A widely used pharmaceutically acceptable salt of clavulanic acid is potassium clavulanate, which is commercially co-formulated with the β-lactam antibiotic amoxycillin, generally in the form of amoxycillin trihydrate, in formulations for oral administration, such as compacted tablets, granules etc..

Some incidence of gastrointestinal intolerance have been observed in patients to whom clavulanate, such as potassium clavulanate, has been administered. This intolerance is manifested in various ways, which may be a result of intestinal fluid accumulation. The precise cause of this intolerance is not understood, and many causes have been suggested. Whatever the cause, the intolerance is seen as a self - limiting nuisance which does not normally prejudice the use of clavulanate, in view of the substantial counter balancing benefits of clavulanate in combating bacterial resistance.

Co-formulations of clavulanate with various substances have been investigated. WO 93/00898 discloses formulations of potassium clavulanate with succinic acid and disodium succinate, in which the latter two compounds are used to buffer the pH when the formulation is made up into aqueous solution, with the intention of improving solution stability. An effervescent formulation which is a chewable tablet which includes clavulanate is disclosed in EP 0396335 A, which uses tartaric, citric or malic acid as the acid component of an effervescent couple together with an alkali metal carbonate or bicarbonate. WO 92/19227 discloses compacted tablet formulations which incorporate sodium starch glycollate as a disintegrant at low ratios with the clavulanate.

Numerous pharmaceutical formulations based upon a variety of therapeutic approaches which aim to alleviate gastrointestinal symptoms of various kinds are known. Citrate salts are known for use in rehydrating formulations. US 3873695 discloses a veterinary rehydrating formulation which comprises 8-hydroxyquinoline, an astringent based upon bismuth or aluminium salts, and a rehydrating agent selected from the magnesium, sodium, potassium or calcium salts of organic acids.

It is an object of this invention to provide formulations including clavulanate, for oral administration, having reduced gastrointestinal intolerance.

The present invention is based upon a novel effect observed with co-formulations or co-administrations of clavulanate with salts and salt-like derivatives of organic acids, and novel formulations based upon this effect.

According to this invention, a solid pharmaceutical formulation for oral administration is provided, comprising in combination clavulanate and a pharmaceutically acceptable organic acid or a pharmaceutically acceptable salt-like derivative thereof or components which can react together to form such a salt-like derivative, with the exclusion: of succinic acid; of tartaric acid, citric acid or malic acid when these acids form a component of an effervescent couple with an alkali metal carbonate or bicarbonate in a chewable tablet; of the combination of disodium succinate and succinic acid; and of sodium starch glycollate in a ratio sodium starch glycollate : clavulanate of $< 1 : 1.4$.

The invention also provides a method of use of clavulanate, and a pharmaceutically acceptable organic acid or a pharmaceutically acceptable salt-like derivative thereof or such components, subject to the abovementioned exclusion, together in the manufacture of a solid antibacterial medicament formulation.

The invention also provides a method for the preparation of a pharmaceutical formulation as defined above, which method comprises admixing the combination of clavulanate and the said pharmaceutically acceptable organic acid and/or a pharmaceutically acceptable salt-like derivative thereof or such components.

The invention also provides a pharmaceutical formulation as defined above for use as an active therapeutic substance, particularly in the treatment of bacterial infections in humans or animals.

The invention also provides a method of suppressing the gastro intestinal intolerance associated with oral dosing of clavulanate-containing products, the method comprising oral co-administration of clavulanate in combination with a pharmaceutically acceptable organic acid or a pharmaceutically acceptable salt-like derivative thereof or components which can react together to form such a salt-like derivative.

The invention also provides a pharmaceutical formulation including clavulanate, in which the gastro intestinal intolerance associated with oral dosing of clavulanate-containing products, is suppressed by a pharmaceutically acceptable organic acid or a pharmaceutically acceptable salt-like derivative thereof.

The invention also provides a method of treatment of bacterial infections in humans, which comprises the administration to a patient in need of treatment an effective amount of a pharmaceutical formulation as defined above.

The solid pharmaceutical formulations of this invention include tablets, pills, granules, powders etc., including such solid formulations which are intended to be reconstituted to form liquid suspensions for administration to patients, and powder

or granulate formulations which are intermediate products for subsequent compaction into tablets. A preferred solid formulation is a compacted tablet formulation, for example made by compaction of powdered and/or granulated ingredients.

The term "salt-like derivative" refers to salts themselves, and to derivatives of the acid in which acid groups in the acid are ionically associated with cations in any way..

In the formulations and methods of this invention, the clavulanate is preferably the potassium salt of clavulanic acid, ie potassium clavulanate. Salts of clavulanic acid are very hygroscopic. Therefore potassium clavulanate should be handled under dry conditions, preferably under conditions of low relative humidity, e.g. 30% RH or less, in the manufacture of formulations of this invention.

In the formulations and methods of this invention a single pharmaceutically acceptable organic acid or a single pharmaceutically acceptable salt-like derivative thereof may be used, or two or more of such may be used in combination.

When the formulation of the invention comprises clavulanate and a pharmaceutically acceptable organic acid the organic acid is preferably a pharmaceutically acceptable mono-carboxylic acid, or a pharmaceutically acceptable solid poly-carboxylic acid.

The formulations of this invention are solid formulations, and therefore preferred pharmaceutically acceptable organic acids such as mono- and poly-carboxylic acids when used as the free acids in the formulation and method are solid acids.

Suitable generic classes and specific examples of pharmaceutically acceptable monocarboxylic acids include solid alkyl mono- and poly- carboxylic acids and aryl mono- and poly- carboxylic acids; pharmaceutically acceptable aminoacids such as glycine; and macromolecular carboxylic acids which include a macromolecular system such as a carbohydrate or polypeptide system, such as pectic acid.

Preferably the formulation of the invention comprises in combination clavulanate and one or more pharmaceutically acceptable salts of one or more carboxylic acids.

Suitable generic classes and specific examples of salts of the abovementioned pharmaceutically acceptable organic, e.g carboxylic, acids include salts with pharmaceutically acceptable cations, particularly cations of Group I or II metals, e.g. sodium, potassium, calcium or magnesium. When the organic acid includes two or more carboxylate groups one, some or all of these may form salts with the cation, for example forming acid salts in which some carboxylate groups remain associated with their acid proton, and also if there are more than one acid group these may all form salts with the same or different cation. When the cation has two

or more positive charges it may ionically associate in the salt-like derivative with two same or different anions of the organic acid.

Suitable generic classes of salts of pharmaceutically acceptable carboxylic acids include salts of the following generic classes and specific examples of carboxylic acids: lower, preferably with a C_{1-10} alkyl chain length or alkyl group size alkylcarboxylic acids, e.g. with a straight, branched or cyclic alkyl chain, e.g. acetic acid, propionic acid, butyric acid, pentanoic acid, hexanoic acid, heptanoic acid and octanoic acid; higher alkylcarboxylic acids such as those with a C_{10-25} carbon chain such as stearic, palmitic, oleic etc. acid; lower, e.g C_{1-12}, mono- or poly- hydroxy mono- and poly- carboxylic acids, which may contain one or more, e.g. up to three, carboxylic acid groups and one or more, e.g up to six, preferably up to three, hydroxy groups such as citric acid, lactic acid, malic acid, gluconic acid and tartaric acid; polycarboxylic acids which may for example contain up to three, for example two, carboxylic acid groups such as C_{1-10} alkyl polycarboxylic acids such as succinnic acid, adipic acid and malonic acid; carboxylic acids containing one or more C=C units or C=O groups (additional to those in the carboxylate group) such as alkylene mono- or poly- carboxylic acids, which may for example contain two or three carboxylic acid groups, for example maleic acid, fumaric acid, levulinic acid and sorbic acid; amino- and polyamino-, for example diamino, mono- or poly- carboxylic acids such as those including one or more carboxylate groups linked into the molecule via an amino group, for example aminoalkyl carboxylic acids and alkylene, e.g C_{2-8} alkylene, diamine tetra-alkanoic acids such as ethylene-diaminetetraacetic acid ("EDTA"), and macromolecular carboxylic acids which include a macromolecular system such as a carbohydrate, e.g. starch, or polypeptide, e.g. protein, system, such as pectic acid, caseinic acid and alginic acid, and starch glycollate salts.

Suitable generic classes and specific example of salts of aromatic acids include salts of monocyclic, and polycyclic aryl, e.g. naphthyl carboxylic acids in which the aryl ring system(s) may be substituted, and in which the one or more carboxylate groups may be linked to the aryl ring(s) either directly or by means of linking groups such as alkyl chains, such as benzoic acid and 6-methoxy-α-methyl-2-naphthalene acetic acid.

Suitable generic classes and specific examples of salts of other types of organic acid are pharmaceutically acceptable compounds containing a (>C=O)-O- group having acid character, such as internally esterified compounds such as ascorbic acid. Also included are organic acids which comprise an organic moiety such as an alkyl or aryl system (e.g. as defined above) combined with an inorganic acid group such as a phosphoric or sulphonic acid group, such as phytic acid (1, 2, 3, 4, 5, 6-cyclohexanehexolphosphoric acid).

Preferred salts are therefore sodium, potassium, magnesium but particularly calcium, salts of lower alkyl mono- and poly- carboxylic acids, lower mono- or poly- hydroxy mono- and poly- carboxylic acids, and monocyclic carboxylic acids with an unsubstituted ring.

Suitable specific examples of such salts include: calcium acetate, calcium lactate, calcium propionate, calcium caseinate, calcium ascorbate, calcium gluconate, calcium tartrate, calcium malate, calcium citrate, calcium maleate, calcium benzoate, calcium pectate, calcium sorbate, calcium stearate, calcium levulinate, calcium succinate, sodium lactate, trisodium citrate (e.g in anhydrous form), disodium hydrogen citrate, sodium propionate, sodium stearate, tripotassium citrate, sodium starch glycollate, calcium phytate, disodium edetate, sodium acetate and magnesium lactate. Such salts may be used in their anhydrous or hydrated forms. For example calcium citrate USP is the tetrahydrate, calcium lactate is known as a pentahydrate, calcium propionate is known as a mono- and a tri-hydrate, and calcium succinate is known as a trihydrate.

Preferred salts are calcium citrate, calcium lactate, calcium propionate, calcium benzoate, calcium succinate, sodium lactate, trisodium citrate, disodium hydrogen citrate, sodium benzoate, tripotassium citrate, and magnesium lactate, particularly calcium citrate and calcium lactate.

In the formulations and methods of the invention the pharmaceutically acceptable salt-like derivative of the organic acid may be used as such, or additionally or alternatively the salt-like derivative may be generated in situ by reaction of components such as an acid or base such as an alkali metal or alkaline earth metal hydroxide, carbonate or hydrogen carbonate which together, e.g. in contact with water, form the derivative. When used in this way, the components may form an effervescent couple, e.g. comprising a solid carboxylic acid such as citric acid, tartaric acid, malic acid, adipic acid, fumaric acid or an acid salt thereof such as sodium hydrogen citrate, and a carbonate such as calcium carbonate, sodium carbonate or sodium hydrogen carbonate. In the effervescent chewable tablet of EP 0396335 A the citric acid / sodium bicarbonate effervescent couple is present solely for taste masking.

In the above formulations and methods the organic acid and/or a pharmaceutically acceptable salt-like derivative thereof or components which can react together to form such a salt-like derivative may be used together with, e.g. coformulated with in a formulation, a pharmaceutically acceptable acid neutralising material. The term "acid neutralising material" used herein includes pharmaceutically acceptable alkalis and bases, i.e. compounds which can potentially combine with acids to produce a salt of the acid plus water. More specifically the term includes materials normally referred to as "antacids" i.e. having the ability to

neutralise gastric acidity.

Suitable generic classes and specific examples of acid neutralising materials include the following generally water insoluble materials: Group II metal carbonates, hydrogen carbonates, oxides (other than calcium oxide), hydroxides (other than calcium hydroxide) and silicates, such as magnesium carbonate, calcium carbonate and calcium silicate; Group III metal carbonates, hydrogen carbonates, oxides, hydroxides and silicates, such as aluminium carbonate, aluminium hydrogen carbonate, aluminium oxide, aluminium hydroxide and aluminium silicate (e.g. Kaolin). Such materials may be used singly or in mixtures with other acid neutralising materials, for example a magnesium carbonate/magnesium hydroxide mixture, for example that having the overall stoichiometry $(MgCO_3)_4\ Mg(OH)_2\ 5H_2O$.

Preferred acid neutralising materials are calcium carbonate and magnesium carbonate. It should be noted however that magnesium salts can themselves cause diarrhea, and the use of magnesium compounds in quantities known to cause diarrhea should be avoided.

The combinations calcium citrate + calcium carbonate, calcium lactate + calcium carbonate, calcium lactate + magnesium carbonate, and calcium lactate + calcium citrate + calcium carbonate are particularly preferred.

In the above formulations and method the organic acid and/or a pharmaceutically acceptable salt-like derivative thereof or components which can react together to form such a salt-like derivative may be used together with, e.g. coformulated with in a formulation, a pharmaceutically acceptable adsorbent material. Some of the Group II metal carbonates, hydrogen carbonates, oxides, hydroxides and silicates, Group III metal carbonates, hydrogen carbonates, oxides, hydroxides and silicates mentioned above have adsorbent properties in addition to their acid neutralising properties and in the formulations and methods of this invention may additionally or alternatively function as adsorbent materials. Also some forms of aluminium oxide, aluminium hydroxide and aluminium silicate (e.g. Kaolin) which may indeed have little or no acid neutralising property; molecular sieves, celluloses, Group II/III metal silicates such as calcium aluminosilicates and other clays, and charcoal may for example be used as adsorbent materials. Such materials may be used singly or in mixtures with other acid neutralising materials and/or adsorbent materials.

In the above formulations and method the organic acid and/or a pharmaceutically acceptable salt-like derivative thereof or components which can react together to form such a salt-like derivative may be used together with, e.g coformulated with in a formulation, a pharmaceutically acceptable methacrylic copolymer. Suitable generic classes and specific examples of pharmaceutically

acceptable methacrylic acid copolymers are those described in the USP 22/NF 17, and such polymers of types A, B and C as described therein may be suitable. Suitable generic classes and specific examples of pharmaceutically acceptable methacrylic acid copolymer are known polymers which are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, for example having a molar ratio of such ammonium groups : remaining (meth)acrylic esters of 1 : $\geq$ 10, for example around 1 : 20 or 1 : 40, and with a mean molecular weight of around 150000. Such polymers correspond to USP/NF 2 "Ammonio methacrylate copolymers, Type A and Type B". Further suitable generic classes and specific examples of pharmaceutically acceptable methacrylic acid copolymer are known polymers which are copolymers, anionic in character, based on methacrylic acid and methyl methacrylate, for example having a ratio of free carboxyl groups : methyl-esterified carboxyl groups of 1 : >3, e.g around 1 : 1 or 1 : 2, and with a mean molecular weight of 135000.

Such polymers are sold under the trade name Eudragit ™, such as the Eudragit L series e.g. Eudragit L 12.5 ™, Eudragit L 12.5P ™, Eudragit L100 ™, Eudragit L 100-55 ™, Eudragit L-30 D ™, Eudragit L-30 D-55 ™, the Eudragit S ™ series e.g. Eudragit S 12.5, Eudragit S 12.5P ™, Eudragit S100 ™, the Eudragit NE™ series e.g Eudragit NE 30D ™, the Eudragit RL ™ series, e.g. Eudragit RL 12.5 ™, Eudragit RL 100 ™, Eudragit RL PO ™, Eudragit RL 30D ™, and the Eudragit RS ™ series e.g. Eudragit RS 12.5 ™, Eudragit RS 100 ™, Eudragit RS PO™, and Eudragit RS 30D™ . Some of these polymers are enteric polymers (the term "enteric polymer" is a term of the art referring to a polymer which is preferentially soluble in the less acid environment of the intestine relative to the more acid environment of the stomach), for example having a solubility in aqueous media at pH 5.5 and above.

Other suitable pharmaceutically acceptable polymers include for example methyl acrylate-methacrylic acid copolymer, methacrylate-methacrylic acid-octyl acrylate copolymer, etc. These may be used either alone or in combination, or together with other polymers than those mentioned above.

In the above formulations and methods, the clavulanate is preferably also co-formulated with an antibiotic compound. The antibiotic compound is suitably a β-lactam antibiotic such as penicillins, which term as used herein includes antibiotic compounds having a nucleus derived from the penicillin ring system, such as penems and carbapenems; or cephalosporins, which term as used herein includes antibiotic compounds having a nucleus derived from the cephalosporin ring system, such as carbacephs. A preferred β-lactam antibiotic is amoxycillin, e.g. in the form amoxycillin trihydrate or the sodium salt of amoxycillin, for example the anhydrous crystalline form of sodium amoxycillin disclosed in EP 0131147 A.

Other suitable antibiotics include those suitable for oral admistration selected from: ampicillin, apalcillin, aspoxicillin, azidocillin, azlocillin, aztreonam, benzylpenicillin, bacampicillin, carbenicillin, cloxacillin, cyclacillin, dicloxicillin, epicillin, flucloxacillin, lenampicillin, mecillinam, methicillin, mezlocillin, phenoxymethylpenicillin, piperacillin, pivampicillin, propicillin, sulbenicillin, talampicillin, ticarcillin, cefaclor, cefadroxil, cefatrizine, cefclidine, cefamandole, cefazolin, cefbuperazone, cefcanel daloxate, cefdinir, cefepime, cefetamet pivoxil, cefixime, cefminox, cefminoxime, cefmetazole, cefonicid, cefoperazone, cefotaxime, cefotetan, cefotiam, cefotiam hexetil, cefoxitin, cefpimizole, cefpiramide, cefrirome, cefpodoxime proxetil ,cefprozil, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone, cefuroxime axetil, cefuroxime, cephacetrile, cephalexin, cephaloridine, cephalothin, cephamanadole nafate, cephapirin, cephoperazone, cefsulodin, cefuzonam, cephradine, loracarbef, DQ 2556, ME1207, S-1006, SCE-2787 and moxalactam.

Such a formulation which includes an antibiotic compound is effective as a therapeutic or prophylactic treatment for bacterial infections.

The weight ratio clavulanate : antibiotic compound in the formulations and methods of this invention may vary within a wide range, e.g. 1:1 to 1:30, expressed in terms of the free acids. In the case of amoxycillin the said ratio may for example be between 1:1 to 1:15, for example 1:1 to 1:12, for example between 1:1 to 1:8, for example 1: 4 to 1:7 by weight.

A preferred formulation of the invention is therefore one which contains potassium clavulanate, amoxycillin in the form of its trihydrate or as sodium amoxycillin, within the weight ratio range clavulanate : amoxycillin 1 : 2 to 1 : 12, for example 1 : 4 to 1: 8.

It is generally preferred to administer the pharmaceutically acceptable organic acid or a pharmaceutically acceptable salt-like derivative thereof or components which can react together to form such a salt-like derivative at, before or around the same time as the administration of the clavulanate. In the formulations and methods of the present invention the clavulanate, the optional antibiotic material, and the pharmaceutically acceptable organic acid or a pharmaceutically acceptable salt-like derivative thereof or components which can react together to form such a salt-like derivative are consequently preferably formulated together for oral administration, and are preferably administered together by this route. Alternatively the clavulanate and optional antibiotic material may be formulated and/or administered together and the pharmaceutically acceptable organic acid or a pharmaceutically acceptable salt-like derivative thereof or components which can react together to form such a salt-like derivative may be separately formulated for oral administration and separately orally administered.

The constituents comprising such an oral formulation, ie clavulanate, pharmaceutically acceptable organic acid(s) and/or a pharmaceutically acceptable salt-like derivative(s) thereof or components which can react together to form such a salt-like derivative may be formulated for oral administration in various ways.

The constituents may for example be formulated simply as a dry powder or granules comprising the constituents, and methods of preparing such a formulation will be apparent to those skilled in the art. Such powders or granules may be presented for example in a dry form in a sachet or capsules. Alternatively the constituents may be formulated into a compacted tablet, for example including conventional excipients such as fillers, diluents, compaction aids, disintegrants, lubricants, wetting agents, flavours, colourants etc. as are known in the art.

Such tablets may also include an effervescent couple, and/or a chewable base. Such tablets may be made by processes well known in the art, for example blending of powdered constituents, granulation eg by slugging or roller compaction, then compaction into a tablet form in a conventional tablet press. Such sachets, capsules or tablets may suitably comprise a unit dosage form, each containing a unit dose of the active constituents.

Alternatively the formulation may be provided as a dry product for reconstitution as a liquid formulation with water or an appropriate vehicle before use.

When the formulations of this invention are presented in unit dosage form, the amount of clavulanate and any antibiotic compound such as amoxycillin included in the formulation may be generally the same as that contained in known formulations containing these. Typically therefore the formulation may contain from 12.5 to 1000mg (expressed as the free acid), preferably from 12.5 to 250mg of clavulanate, e.g. 12.5, 25, 50, 75, 100, 125, 150, 200 or 250mg of potassium clavulanate. Typically the amount of the antibiotic, for example amoxycillin may be in the range from 125 to 3000 mg (expressed as the free acid), suitably from 125 to 1000mg. Suitably the antibiotic compound may be used in a weight proportion of the overall solid dosage form, such as a compacted tablet, similar to that in which it is conventionally used. For example the antibiotic may comprise 5 to 80 wt%, e.g. 50 to 80 wt%, and the clavulanate may comprise 0.5 to 30 wt%, of the solid dosage form such as a compacted tablet.

Suitable quantities of the pharmaceutically acceptable organic acid and/or a pharmaceutically acceptable salt-like derivative thereof or components which can react together to form such a salt-like derivative for use in the formulations and methods of the present invention vary between wide limits and may be determined by experimentation, for example by clinical trials observing symptoms of gastrointestinal intolerance with various combinations of clavulanate, antibiotic and

the pharmaceutically acceptable organic acid and/or a pharmaceutically acceptable salt-like derivative thereof or components which can react together to form such a salt-like derivative.

It is generally desirable to limit the weight of a pharmaceutical tablet intended for swallowing by a patient to a reasonable size to facilitate swallowing, e.g around 1-2 g maximum per tablet, 1.5 g generally being a comfortable maximum in practice. Consequently the total quantity of the pharmaceutically acceptable organic acid or a pharmaceutically acceptable salt-like derivative thereof or components which can react together to form such a salt-like derivative included in a single tablet may suitably be around 25 - 500 mg, for example around 100 - 300 mg, and for example these quantities may be combined with 100 - 300 mg of the above-described acid neutralising and/or adsorbent materials. Suitably the quantity of the pharmaceutically acceptable organic acid and/or a pharmaceutically acceptable salt-like derivative thereof or components which can react together to form such a salt-like derivative may comprise 0.5 - 50 wt% of the solid dosage form such as a compacted tablet, for example 10 - 50 wt%.

For example reduction of gastrointestinal intolerance may be observed on oral coadministration of clavulanate together with amoxycillin and the above-mentioned pharmaceutically acceptable organic acid and/or a pharmaceutically acceptable salt-like derivative thereof or components which can react together to form such a salt-like derivative, such as calcium propionate, calcium lactate, calcium citrate or sodium lactate, in ratios of clavulanate : pharmaceutically acceptable organic acid and/or a pharmaceutically acceptable salt-like derivative thereof in the range 10 : 1 to 1 : 10, relative to the gastrointestinal intolerance observed with the oral administration of these amounts of clavulanate and amoxycillin without the salt-like derivative. For example the weight ratio potassium clavulanate : pharmaceutically acceptable organic acid and/or a pharmaceutically acceptable salt-like derivative thereof or components which can react together to form such a salt-like derivative, such as calcium citrate or calcium lactate, may conveniently but not exclusively range between 1 : 3 and 3 : 1, suitably between 1 : 2 and 2 : 1 inclusive in the solid formulations of this invention.

The remaining bulk of the dosage form may be made up to 100 wt% by the above mentioned excipients, which may be used in conventional proportions as known in the art. General methods of making a compacted tablet comprising potassium clavulanate and an antibiotic such as amoxycillin trihydrate, together with the abovementioned excipients are well known, for example as disclosed in GB 2005538A and WO92/19227 which disclose methods and formulations such as dry compaction of powders, granulation of the amoxycillin and clavulanate and compaction of the granules or inclusion of the powdered ingredients or granules in a

sachet.

The invention will now be described by way of example only with reference to the following examples which discuss the effect of various compounds and combinations of compounds on fluid accumulation in the gastro-intestinal system of the rat. This is accepted as a guide to gastro intestinal intolerance as manifested by diarrhea, a reduction in the amount of fluid accumulation being generally regarded as indicating a likelihood of reduction of diarrhea.

Example 1: Evaluation of Effects of Agents on intestinal and gastric fluid secretion in the gastro-intestinal system of the rat.

Materials:

Potassium clavulanate and amoxycillin trihydrate (SB Pharmaceuticals, Bristol, Tennessee) were prepared in water.

Enteropooling Assay:

Male Sprague-Dawley rats weighing 200-300 g were housed in individual wire-bottomed cages to restrict coprophagia. Animals were food deprived for 24 hr prior to experimentation with water provided *ad libitum*. Using a protocol similar to that described previously for dimethyl PGE_2 (Robert et al., 1976; Fondacaro et al., 1989), test agents dissolved or suspended in Mili-Q water were administered to conscious rats by gavage at a dose volume of 1 ml. Animals were sacrificed at 60 min following dosing. The abdomen was opened and the small intestine clamped at the pyloric sphincter and ileocaecal junction; the intestinal segment thus isolated was carefully removed from the abdominal cavity, the length measured and then weighed, emptied of its fluid conter and reweighed. Enteropooling is expressed as mg. of fluid / cm. of intestine.

Gastric Fluid Accumulation:

Gastric fluid secretion or gastric enteropooling was determined according to the following methods. Male Sprague-Dawley rats weighing 200-300 g were housed in individual wire-bottomed cages to restrict coprophagia. Animals were food deprived for 24 hr prior to perimentation with water provided *ad libitum* est agents dissolved or suspended in water were administered to conscious rats by gavage at a dose volume of 1 ml. Animals were sacrificed at a standard time, usually 60 min, following dosing. The abdomen was opened and the stomach clamped at the pyloric sphincter and lower esophagal sphincter; the stomach thus isolated was carefully removed

from the abdominal cavity, weighed, emptied of its fluid contents and reweighed. Enteropooling is expressed as total grams of fluid.

Assay results of intestinal enteropooling and stomach fluid accumulation are tabulated below. (Amox. = amoxycillin, K.clav. = potassium clavulanate, Eud. = Eudragit).

Agent (mg/kg)	Intestinal Mean	SEM	n	Stomach Mean	SEM	n
Water	7.58	0.27	71	0.27	0.04	10
amoxycillin (200)	*8.84*	*0.61*	*11*	*0.29*	*0.06*	*5*
K. clavulanate (100)	*21.29*	*0.39*	*182*	*1.23*	*0.08*	*109*
Effect of agents:						
K. clavulanate (100)	*21.29*	*0.39*	*182*	*1.23*	*0.08*	*109*
K. clavulanate (100)+						
+Ca lactate (100)	13.07	0.86	24	0.63	0.09	22
+Ca lactate (50)	17.10	1.09	15	0.89	0.13	14
+Ca lactate (25)	16.64	1.20	15	1.07	0.20	14
+Na lactate (100)	14.65	1.02	10	0.48	0.10	10
+Mg lactate (100)	11.96	0.95	5	0.61	0.09	5
+Ca citrate (200)	14.84	1.77	5	0.67	0.06	4
+Ca citrate (100)	17.38	1.00	19	0.53	0.09	18
+Tri-Na citrate (100)	17.96	0.81	15	0.57	0.07	14
+Di-Na hydrogen citrate (100)	18.30	2.07	10	0.59	0.08	9
+Tri-K citrate (100)	18.86	1.53	5	0.43		2
+Ca benzoate (100)	14.32	0.85	15	0.91	0.17	15
+Na benzoate (100)	14.07	1.60	5	1.16	0.27	4
+Ca propionate (85)	15.91	1.27	6			
+Ca succinate (85)	18.21	1.21	10	0.68	0.24	4
+Ca malate (100)	19.11	1.90	5	1.11	0.34	5
+Ca levulinate (100)	17.81	1.02	15	0.56	0.12	13
+Na stearate (50)	19.96	2.03	5	0.95	0.14	5
+Glycine (32)	19.36	1.97	6			
+Ca caseinate (100)	17.05	1.48	10	1.07	0.18	9
+Ca ascorbate (100)	20.43	1.63	10	0.59	0.10	10
+Ca tartrate (100)	18.00	1.24	9	0.83	0.14	9
+Na starch glycollate (100)	19.66	1.33	10	0.65	0.12	10
+Ca lact. (100)/Eud L30(D) (300)	16.09	0.99	5	0.86	0.25	5
+Ca lact.(50) / $CaCO_3$ (50)	12.31	0.66	5	0.48	0.05	5
+Ca lact.(25) / $CaCO_3$ (25)	13.74	0.43	4	0.58	0.11	5
+Ca lact.(12.5) / $CaCO_3$ (12.5)	21.82	3.19	5	0.44	0.07	4
+Ca lactate(50) / Ca citrate (50)	14.56	1.36	4	0.25	0.04	3
+Ca lactate(25) / Ca citrate (25)	16.02	2.28	5	0.41	0.05	5
+Ca lactate(12.5 / Ca citrate (12.5)	17.34	1.37	5	0.60	0.09	4

Agent (mg/kg)	Intestinal Mean	SEM	n	Stomach Mean	SEM	n
+Ca lactate / $CaCO_3$ / Ca citrate (17/17/17)	14.87	0.67	4	0.44	0.08	5
+Ca lactate / $CaCO_3$ / Ca citrate (8/8 /8)	16.95	1.58	4	0.83	0.18	3
+Ca lactate (50) / $MgCO_3$ (50)	11.71	0.63	4	0.47	0.09	3
+$NaHCO_3$ (100) / citric acid (100)	17.25	2.29	5	0.62	0.20	5
+$NaHCO_3$ (100) / citric acid (50)	16.34	0.92	5	0.94	0.20	5
Amox. / K.clav. (200/100)	*25.57*	*0.50*	*133*	*1.39*	*0.13*	*31*
Amox. / K.clav. (200/100) +						
+Ca propionate (43)	23.03	3.05	5			
+Ca propionate (85)	15.68	0.90	15	0.71	0.14	10
+Ca propionate (100)	19.32	0.86	5	1.06	0.36	5
+Na propionate (86)	24.56	1.92	5			
+Na propionate (172)	23.27	2.66	5			
+Ca succinate (85)	19.53	1.03	5			
+Ca acetate (86)	23.45	1.17	5	0.81	0.04	5
+Ca lactate (100)	17.49	1.06	5	0.99	0.16	5
+Ca citrate (100)	19.82	1.44	10	1.02	0.20	8
+Ca benzoate (100)	17.89	1.58	10	1.47	0.17	9
+Ca lact. (25) / $CaCO_3$ (25)	16.59	2.20	5	0.77	0.21	5
+Ca lact. (12.5) / $CaCO_3$ (12.5)	16.59	2.20	5	0.77	0.21	5
+Ca lact. (25) / Ca citrate (25)	21.02	2.11	5	1.06	0.28	5
+Ca lact. (12.5) / Ca citrate (12.5)	19.19	3.64	5	1.14	0.29	5
+Ca lactate / $CaCO_3$ / Ca citrate (17/17/17)	22.46	2.43	5	0.56	0.09	5
+Ca lactate / $CaCO_3$ / Ca citrate (8/8 /8)	22.44	2.59	5	1.32	0.18	5
+Ca propionate. (85) /Eud. (300)	12.98	0.85	5	1.07	0.15	5
+Ca propionate. (85) /Eud. (600)	11.01	2.01	5	1.12	0.20	5

Example 2: Tablet Formulations.

Two tablet formulations of this invention suitable for administration to humans are listed below.

Formulation 1:

Component	mg per tablet	wt%
Amoxycillin trihydrate	875.00[1]	58.33
Potassium clavulanate	125.00[1]	8.33
Calcium citrate USP	125.00	8.33
Calcium carbonate USP[2]	125.00	8.33
Sodium starch glycollate NF	30.00	2.00
Magnesium stearate NF	15.00	1.00
Microcrystalline cellulose NF	qsad 1500.00	100

Formulation 2:

Component	mg per tablet	wt%
Amoxycillin trihydrate	500.00[1]	47.6
Potassium clavulanate	125.00[1]	11.9
Calcium citrate USP	125.00	11.9
Calcium carbonate USP[2]	125.00	11.9
Sodium starch glycollate NF	21.00	2.0
Magnesium stearate NF	10.50	1.0
Microcrystalline cellulose NF	qsad 1050.00	100.0

Note: [1] weight expressed as free acid equivalent.
[2]anhydrous

These formulations were made into compacted tablets using standard methods known in the art, suitably those disclosed in GB 2005538A. Equivalent tablets were also made containing 125 mg calcium lactate pentahydrate instead of the calcium citrate, and 250 mg of calcium citrate USP or 250mg calcium lactate penytahydrate instead of the combined 250 mg of calcium citrate plus calcium carbonate mentioned in Formulations 1 and 2.

Claims:

1. A solid pharmaceutical formulation for oral administration, comprising in combination clavulanate and a pharmaceutically acceptable organic acid or a pharmaceutically acceptable salt-like derivative thereof or components which can react together to form such a salt-like derivative, with the exclusion: of succinic acid; of tartaric acid, citric acid or malic acid when these acids form a component of an effervescent couple with an alkali metal carbonate or carbonate in a chewable tablet; of the combination of disodium succinate and succinic acid; and of sodium starch glycollate in a ratio sodium starch glycollate : clavulanate of $< 1 : 1.4$.

2. A solid pharmaceutical formulation according to claim 1 characterised in that the clavulanate is potassium clavulanate.

3. A solid pharmaceutical formulation according to claim 1 comprising clavulanate and one or more pharmaceutically acceptable solid mono-carboxylic acids, or one or more pharmaceutically acceptable solid poly-carboxylic acids.

4. A solid pharmaceutical formulation according to claim 3 characterised in that the monocarboxylic acid is selected from solid alkyl mono- and poly- carboxylic acids and aryl mono- and poly- carboxylic acids; pharmaceutically acceptable aminoacids; and macromolecular carboxylic acids which include a macromolecular system.

5. A solid pharmaceutical formulation according to claim 1 comprising in combination clavulanate and one or more pharmaceutically acceptable salts of one or more carboxylic acids.

6. A solid pharmaceutical formulation according to claim 5 characterised in that the one or more pharmaceutically acceptable salts of one or more carboxylic acids is a salt of a Group I or II metal.

7. A solid pharmaceutical formulation according to claim 5 characterised in that the one or more salts of pharmaceutically acceptable carboxylic acids are selected from salts of lower carboxylic acids, higher alkylcarboxylic acids, mono- or poly-hydroxy mono- and poly- carboxylic acids, which may contain one or more carboxylic acid groups and one or more hydroxy groups, polycarboxylic acids, carboxylic acids containing one or more C=C units or C=O groups additional to those in the carboxylate group, amino- and polyamino- carboxylic acids,

macromolecular carboxylic acids which include a macromolecular system, and monocyclic and polycyclic aryl carboxylic acids in which the aryl ring system(s) may be substituted, and in which the one or more carboxylate groups may be linked to the aryl ring(s) either directly or by means of linking groups.

8. A solid pharmaceutical formulation according to claim 7 characterised in that the one or more salts of pharmaceutically acceptable carboxylic acids are selected from salts of acetic acid, propionic acid, butyric acid, pentanoic acid, hexanoic acid, heptanoic acid and octanoic acid stearic, palmitic acid, olei cid, citric acid, lactic acid, malic acid, gluconic acid, tartaric acid, succinnic acid, adipic acid, malonic acid, maleic acid, fumaric acid, levulinic acid, sorbic acid, ethylene-diaminetetraacetic acid ("EDTA"), pectic acid, caseinic acid, alginic acid, starch glycollate salts, benzoic acid, 6-methoxy-α-methyl-2-naphthalene acetic acid, ascorbic acid and phytic acid (1, 2, 3, 4, 5, 6-cyclohexanehexolphosphoric acid).

9. A solid pharmaceutical formulation according to claim 8 characterised in that the salt of a Group I or II metal is selected from calcium acetate, calcium lactate, calcium propionate, calcium caseinate, calcium ascorbate, calcium gluconate, calcium tartrate, calcium malate, calcium citrate, calcium maleate, calcium benzoate, calcium pectate, calcium sorbate, calcium stearate, calcium levulinate, calcium succinate, sodium lactate, trisodium citrate (e.g in anhydrous form), disodium hydrogen citrate, sodium propionate, sodium stearate, tripotassium citrate, sodium starch glycollate, calcium phytate, disodium edetate, sodium acetate and magnesium lactate.

10. A solid pharmaceutical formulation according to claim 9 characterised in that the one or more pharmaceutically acceptable salts of one or more carboxylic acids is selected from calcium lactate and calcium citrate, and the combination of calcium lactate and calcium citrate.

11. A solid pharmaceutical formulation according to claim 5 characterised in that the one or more pharmaceutically acceptable salts of one or more carboxylic acids is generated in situ by reaction of components which together form the salt(s).

12. A solid pharmaceutical formulation according to claim 5 characterised in that the one or more pharmaceutically acceptable salts of one or more carboxylic acids is used together with a pharmaceutically acceptable acid neutralising material.

13. A solid pharmaceutical formulation according to claim 12 characterised in

that the acid neutralising material is selected from Group II metal carbonates, hydrogen carbonates, oxides (other than calcium oxide), hydroxides (other than calcium hydroxide) and silicates, Group III metal carbonates, hydrogen carbonates, oxides, hydroxides and silicates.

14. A solid pharmaceutical formulation according to claim 13 characterised in that the acid neutralising material is selected from magnesium carbonate, calcium carbonate, calcium silicate, aluminium carbonate, aluminium hydrogen carbonate, magnesium hydroxide, aluminium oxide, aluminium hydroxide and aluminium silicate and mixtures thereof.

15. A solid pharmaceutical formulation according to claim 5 characterised in that the one or more pharmaceutically acceptable salts of one or more carboxylic acids is used together with a pharmaceutically acceptable adsorbent material.

16. A solid pharmaceutical formulation according to claim 15 characterised in that the pharmaceutically acceptable adsorbent material is selected from the group consisting of Group II metal carbonates, hydrogen carbonates, oxides, hydroxides and silicates, Group III metal carbonates, hydrogen carbonates, oxides, hydroxides and silicates; molecular sieves, celluloses, Group II/III metal silicates, and charcoal

17. A solid pharmaceutical formulation according to claim 12 comprising in combination clavulanate and a combination selected from calcium lactate + calcium carbonate, calcium citrate + calcium carbonate, calcium lactate + magnesium carbonate, and calcium lactate + calcium citrate + calcium carbonate.

18. A solid pharmaceutical formulation according to claim 5 comprising in combination clavulanate and one or more pharmaceutically acceptable salts of one or more carboxylic acids together with a pharmaceutically acceptable methacrylic copolymer.

19. A solid pharmaceutical formulation according to claim 1 characterised in that the clavulanate is co-formulated with an antibiotic compound.

20. A solid pharmaceutical formulation according to claim 19 characterised in that the antibiotic compound is a β-lactam antibiotic.

21. A solid pharmaceutical formulation according to claim 20 wherein the β-lactam antibiotic is amoxycillin.

22. A solid pharmaceutical formulation according to claim 19 wherein the weight ratio clavulanate : antibiotic compound in the formulation is within the range 1:1 to 1:30, expressed in terms of the free acids.

23. A solid pharmaceutical formulation according to claim 22 which contains potassium clavulanate and amoxycillin within the weight ratio range clavulanate : amoxycillin 1 : 2 to 1 : 12.

24. A solid pharmaceutical formulation according to claim 1 characterised in that the clavulanate is potassium clavulanate and the pharmaceutically acceptable salt-like derivative calcium citrate or calcium lactate is used, and the weight ratio clavulanate : pharmaceutically acceptable salt-like derivative ranges between 1 : 3 and 3 : 1 inclusive.

25. A method for the preparation of a pharmaceutical formulation according to claim 1, which method comprises admixing the combination of clavulanate and the said pharmaceutically acceptable organic acid and/or a pharmaceutically acceptable salt-like derivative thereof or components which can react together to form such a salt-like derivative, optionally with an antibiotic.

26. A method of suppressing the gastro intestinal intolerance associated with oral dosing of clavulanate-containing products, the method comprising oral co-administration of clavulanate in combination with a pharmaceutically acceptable organic acid or a pharmaceutically acceptable salt-like derivative thereof or components which can react together to form such a salt-like derivative.

27. A method of treatment of bacterial infections in humans, which comprises the administration to a patient in need of treatment an effective amount of a pharmaceutical formulation according to claim 1.

INTERNATIONAL SEARCH REPORT

Intern .ial Application No
PCT/EP 95/03322

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/43 A61K31/42 //(A61K31/43,31:42,31:19)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 049 061 (BEECHAM GROUP PLC) 7 April 1982 see page 4, column 1-24 see ---	1,2,5-8, 12-16, 18-23
X	EP,A,0 002 312 (BEECHAM GROUP LTD) 13 June 1979 see page 17, line 1-12 ---	1,5-8
X	WO,A,94 16696 (SMITHKLINE BEECHAM PLC ;SMITH GILLIAN MARJORY (GB); THORBURN CHRIS) 4 August 1994 see claims see page 5, paragraph 2 -----	1-27

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 January 1996	12.02.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	LEHERTE C.F.M.

Form PCT/ISA/210 (second sheet) (July 1992)

rnational application No.

PCT/EP 95/03322

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 26-27 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-27
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

In view of the large number of compounds which are defined in the wording of the claims, the search has been performed on the general idea and compounds mentioned in the examples of the description.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inten. nal Application No
PCT/EP 95/03322

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0049061	07-04-82	AU-B-	549321	23-01-86
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		CA-A-	1187796	28-05-85
		GB-A,B	2084016	07-04-82
		JP-B-	1055244	22-11-89
		JP-C-	1568566	10-07-90
		JP-A-	57091921	08-06-82
		US-A-	4537887	27-08-85
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		AU-B-	4121778	08-05-80
		CA-A-	1117532	02-02-82
		JP-A-	54090192	17-07-79
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		EP-A-	0680322	08-11-95